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MINIREVIEWS

New horizons for uncommon mutations in non-small cell lung cancer: *BRAF*, *KRAS*, *RET*, *MET*, *NTRK*, *HER2*

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Abstract

The 2004 discovery of *EGFR* mutations, followed by *ALK* rearrangements, ushered in a targeted therapy era for advanced non-small cell lung cancer (NSCLC). Tyrosine kinase inhibitors targeting gene alterations have substantially improved survival and quality of life for patients with NSCLC. In the last decade, rearrangements of the ROS1 oncogene have been incorporated into healthcare

practice that are applicable to another small subgroup of patients who benefit from similar targeted strategies. Recent genome studies of lung adenocarcinoma have identified other possible therapeutic targets, including *RET*, *NTRK* fusions, *c-MET* alterations, and activating mutations in *KRAS*, *BRAF*, and *HER2,* all with frequencies greater than 1%. Lung cancers harbouring these genome changes can potentially be treated with agents approved for other indications or under clinical development. This review updates the therapeutic arsenal that especially targets those genes.

Key Words: *BRAF*; *NTRK*; *KRAS*; *MET*; *RET*; *HER2*; Non-small cell lung cancer; Targeted therapy; Uncommon mutations

Core Tip: Compared to other types of cancer, non-small cell lung cancer (NSCLC) is highly genetically altered. Outside of *EGFR, ALK,* and *ROS1*, reflecting 15%-20% of clinical practice, other molecular alterations with important recent advances in their therapeutic arsenal and already in phase II/III trials are *BRAF, KRAS, RET, MET, NTRK,* and *HER2*. The goal is to achieve, compared to conventional treatments such as chemotherapy, better symptom control, better response rates, and improved progression-free survival and overall survival in patients with NSCLC.

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INTRODUCTION

Approximately 60% of lung adenocarcinomas harbour molecular alterations in driver oncogenes, with incidence, which varies according to ethnic origin and alteration, as follows: epidermal growth factor receptor (EGFR) mutation, 15%-20%[1]; anaplastic lymphoma kinase (*ALK*) rearrangement, 5%-7%[2]; and c-ros 1 (*ROS1*) rearrangement, approximately 1%[3]. There has been an impressive improvement in survival in response to tyrosine kinase inhibitors (TKIs), which also have a better toxicity profile compared to standard chemotherapy.

The consequent improvement in molecular understanding of non-small cell lung carcinoma (NSCLC) has allowed increasingly exhaustive molecular classification as well as identification of a subset of patients susceptible to specifically targeted therapy. The outcome of massive gene-sequencing platforms with higher throughput than gene-to-gene determinations is that patients can be offered more treatments that more specifically impact on their quality of life and survival. The current recommendation is to carry out a comprehensive molecular analysis using multiplex platforms – next-generation sequencing (NGS) – if available, considering advantages in terms of coverage, time, and a favorable economic profile[4]. NGS is capable of detecting less common or difficult-to-identify oncogenes, such as Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutations (30%-35%), V-raf murine sarcoma viral oncogene homolog B (*BRAF*) mutations (4%-5%), mesenchymal-epithelial transition factor (*c-MET*) alterations, exon 14 insertions and/or amplifications (5%-9%), rearrangements during transfection (*RET*) (1%-2%), human epidermal growth factor receptor 2 (*HER2*) mutations (2%), and neurotrophic receptor tyrosine kinase (*NTRK*) fusions (< 1%)[5]. Identifying these alterations is increasingly important, as new specific drugs in clinical development show promise in terms of modifying the natural history of NSCLC. We focus on direct inhibitors of pathways and their practice-changing results.

BRAF

Present in 2%-3% of NSCLC cases, the *BRAF* mutation is mostly encountered in patients diagnosed with adenocarcinoma[6]. The most common variant is *V600E*, found in 50%-60% of patients with *BRAF*-mutated (*BRAF*m) NSCLC. Not clear is the prognostic value of *BRAF-V600E* compared with non-*V600E* or with the rest of patients with NSCLC[7].

The drugs used to date for this molecular alteration are the same TKIs that have proven to be effective in treating melanoma, a tumour with high *BRAF*m frequency.

Table 1 summarizes the efficacy of the main drugs used to date. The best results have been reported for dabrafenib combined with trametinib, which attempt to block the MAPK pathway at two different sites (*BRAF* and *MEK*), thus overcoming possible tumour resistance to TKIs. The BRF113928 study in patients who received 2-4 Lines of therapy reported an objective response rate (ORR) of 63.2%, and a first-line ORR of 64%[8-12].

However, the absence of comparative data for first and subsequent lines of therapy as currently used for this group of patients means that it is not possible to confirm significant clinical benefit and efficacy over alternative therapies. Dabrafenib and trametinib may therefore be of use for patients for whom standard therapies are not possible or have failed.

Phase II studies are also currently recruiting for the encorafenib + binimetinib (NCT04526782) and cobimetinib + vemurafenib (NCT03178552) combinations.

KRAS

KRAS is the most common mutation in NSCLC, present in up to 30% of adenocarcinomas[13]. In 80% of cases it is located at codon 12, and the most frequent mutation is *KRAS-G12C*, reflected in 13% of all lung adenocarcinomas. It is considered practically exclusive in relation to any other clinical practice drivers, although co-occurrences have been found with alterations in *TP53*, cyclin dependent kinase inhibitor 2A/B (*CDKN2A/B*), *STK11*, and *KEAP1 (*Kelch Like ECH Associated Protein 1)[14].

While *KRAS* has been a therapeutic target for decades, no direct therapeutic option has been established. In recent years, new direct inhibitors of *KRAS-G12C* have emerged. Phase II trial results for sotorasib, an irreversible and highly selective *KRAS-G12C* inhibitor, have positioned it as a major lung cancer milestone for the *KRAS* mutation[15,16]; for 126 included patients, the ORR was 37.1%, there were three complete responses (CRs) and 43 partial responses (PRs), and the disease control rate was 80.6%, for a median progression-free survival (PFS) of 6.8 mo and a good tolerability profile. Based on those data, an application for marketing authorization has been submitted to the FDA and EMA.

In two presentations at the 32nd Symposium on Cancer Therapeutics and Molecular Targets EORTC-NCI-AACR[17,18], investigators from the KRYSTAL-1 phase I and II clinical trial reported that adagrasib clinical activity has been demonstrated in previously treated patients with NSCLC and the *KRAS-G12C* mutation. Promising preliminary data for this drug are to be further evaluated in trials, along with combinations, including with pembrolizumab in the KRYSTAL-7 phase 2 trial (NCT04613596) of untreated patients[19].

RET

RET gene fusions and activating point mutations are primary oncogenic drivers that are usually mutually exclusive with other oncogenic driver alterations[20]. Among the various oncogene drivers in NSCLC, the *RET* gene is involved in various chromosomal rearrangements, found in 1%-2% of all NSCLC patients[21].

Most of the drugs active against *RET* are TKIs. Multikinase inhibitors initially studied in phase II clinical trials include cabozantinib, nintedanib, lenvatinib, vandetanib, and sorafenib, each with a different ORR (Table 2)[22-25].

Selpercatinib (LOXO-292) is a highly selective, potent, central nervous system (CNS)-active, small-molecule *RET* kinase inhibitor. Selpercatinib has nanomolar potency against wild-type *RET* and other *RET* alterations, including the *KIF5B-RET* fusion and *V804M* gatekeeper mutation, in both enzyme and cellular assays, with minimal activity against other kinase and non-kinase targets[26].

In the LIBRETTO-001 phase I/II trial, selpercatinib treatment demonstrated clinically meaningful responses and sustained antitumour activity, for a manageable toxicity profile, in both heavily pre-treated and treatment-naive patients, and including patients with brain metastases and with *RET* fusion-positive NSCLC (intracranial CNS (n = 10/11): ORR 91%). In May 2020, selpercatinib was approved by the FDA under the Accelerated Approval programme for the treatment of *RET*-altered cancers (NSCLC and thyroid cancer)[27].

Pralsetinib (BLU-667) is a novel small-molecule *RET* inhibitor, designed for high potency and selectivity against oncogenic *RET* alterations, including the most frequent *RET* rearrangements (*e.g.*, *KIF5B–RET* and *CCDC6–RET*). The global phase I/II ARROW study has demonstrated broad and durable antitumour activity for pralsetinib in a variety of advanced *RET*-altered solid tumours, including *RET* fusion+ NSCLC. For 354 patients with advanced solid tumours who received pralsetinib as first-line treatment, the ORR was 73%, for a 12% CR rate (n = 26). Treatment-related adverse events were most frequently grade 1-2[28]. Table 2 summarizes the activity of the different TKIs against *RET*.

Table 1 Phase II trials with BRAF inhibitors

Drug	*n*	ORR (%)	PFS (mo)	OS (mo)
Vemurafenib BRAF V600E[8]	62	37.1	6.51	15.38
Vemurafenib V600E[9]	101	0	5.2	10
Vemurafenib non-V600E[9]	17	44.9	NR	NR
Dabrafenib in 2nd line or beyond[10]	78	33.3	5.5	12.7
Dabrafenib + trametinib in 2nd line or beyond[11]	57	63.2	10.2	18.2
Dabrafenib + trametinib en 1st line[12]	36	64	10.9	24.6

ORR: Overall response rate; PFS: Progression free survival; OS: Overall survival; NR: Not reported.

Table 2 Phase II trials with multikinase RET inhibitors

Drug	*n*	ORR	PFS	OS
Cabozantinib[22]	25	28%	5.5 mo	9.9 mo
Vandetanib[23]	18	18%	4.5 mo	11.6 mo
Lenvatinib[24]	25	16%	7.3 mo	NR
Sorafenib[25]	3	0	NR	NR
Selpercatinib[26]	105	64% in platinum chemotherapy pretreated 85% in platinum chemotherapy naïve	90% in response at 6 mo	NR
Pralsetinib[27]	106	61% in platinum chemotherapy pretreated 73% in platinum chemotherapy naïve	NR	NR

ORR: Overall response rate; PFS: Progression free survival; OS: Overall survival; NR: Not reported.

RXDX-105 differs from the other multi-targeted TKIs because it has *RET* activity but limited activity against the vascular endothelial growth factor (*VEGF*) receptors. In *RET* TKI-naive patients, the drug showed modest activity. Subset analysis revealed that the ORR varied by fusion partner. ORRs were 0% (0/20) in the *RET-KIF5B* rearrangement subset (the most common rearrangement) and 67% (6/9) in the *RET*-non-*KIF5B* rearrangement subset[29].

MET

c-MET is an oncogene that encodes a tyrosine kinase receptor whose ligand is hepatocyte growth factor (*HGF*). Alterations in *c-MET* (mutation, amplification, or overexpression) cause abnormal receptor activity that is associated with rapid tumour growth, greater tumour aggressiveness, and resistance to cancer treatments[30].

c-MET amplification is present in 1%-6% of patients with NSCLC. Skipping mutation of exon 14 occurs in 3%-4% of cases, most frequently for non-squamous and sarcomatoid histologies (20%-30%). This alteration occurs most frequently in older patients and in smokers.

Selective and non-selective *c-MET* inhibitors (Tables 3 and 4) are currently available that can impact on survival in patients with NSCLC. The first drug to demonstrate efficacy with this tumour subtype was crizotinib: In the PROFILE 1001 study, the ORR was 32% and PFS was 7.3 mo[31].

Capmatinib is another drug that has been shown to be active: in the GEOMETRY MONO-1 study, the ORR was 41% and PFS was 5.4 mo in previously treated patients; in first-line patients, the ORR was 68% and PFS was 12.4 mo, while ORR was 54% for intracranial activity[32]. In the VISION study, tepotinib achieved an ORR greater than 40%, irrespective of the therapy line, PFS of 8.5 mo, and an ORR of 55% for intracranial activity[33]. Regarding *MET* amplification, TKIs have only significantly benefited tumours with a high level of amplification (*MET/CEP7* > 5), for an ORR of 40% with crizotinib and of 47% with capmatinib.

Amplification, which may appear de novo or as a mechanism of resistance to the targeted treatment of *EGFR* tumours, is present in 4% of cases of progression to first/second generation inhibitors, and in 15% of cases of progression to osimertinib. Being explored, therefore, is the combination of *EGFR*

Table 3 Mesenchymal-epithelial transition factor inhibitors

Drug	MET-specific	Type	Other targets	IC50 (nmol/L)
Crizotinib	No	Ia	ALK, ROS1	22.5
Capmatinib	Yes	Ib	--	0.6
Tepotinib	Yes	Ib	--	3
Salovitinib	Yes	Ib	--	2.1
Bozitinib	Yes	I	--	0.51
Cabozantinib	No	II	RET, ROS1, VEGFR2, KIT	7.8
Merestinib	No	II	TIE-1, AXL, ROS1, DDR1/2, FLT3, MERTK, RON	8.1
Glesatinib	No	II	MET, VEGFR, RON, TIE-2	21.1

IC50: Half maximal inhibitory concentration; MET: Mesenchymal-epithelial transition factor.

Table 4 Clinical trials of mesenchymal-epithelial transition factor inhibitors

Drug	Clinical trial	Phase	Treatment	Objective	Status
Glesatinib	NCT02954991	2	Glesatinib + Nivolumab	ORR	Active, not recruiting
Multi-TKI					
Glesatinib	NCT02544633	2	Glesatinib	ORR	Completed
Multi-TKI					
Merestinib	NCT02920996	2	Merestinib	ORR	Active, not recruiting
Multi-TKI					
Savolitinib	NCT02897479	2	Savolitinib	ORR	Active, not recruiting
Selective-TKI					
Telisotuzumab (ABBV 399)	NCT03574753	2	ABBV-399	ORR	Completed
MET-mab					
JNJ-61186372	NCT02609776	1	JNJ-61186372	ORR, security	Recruiting
EGFR and MET mab					

TKI: Tyrosine kinase inhibitor; mab: Monoclonal antibody; ORR: Overall response rate; MET: Mesenchymal-epithelial transition factor; EGFR: Epidermal growth factor receptor.

inhibitors and *MET* inhibitors.

The TATTON study explored osimertinib combined with savolitinib in patients with NSCLC and mutated *EGFR*. In the group that received initial treatment with a first/second generation inhibitor, the ORR was 52%, while in the group that received osimertinib, the ORR was 25%, for an acceptable toxicity profile[34].

As for immunotherapy, despite the fact that the tumours may present with elevated *PD-L1* expression, the benefit reported for retrospective studies by a French group was limited, at an ORR of 16% and PFS of 3.4 mo[35].

NTRK

The tropomyosin receptor kinase (*TRK*) family consists of three tyrosine kinase receptors – *TRKA, TRKB,* and *TRKC* isoforms, encoded by the *NTRK1, NTRK2,* and *NTRK3* genes, respectively – that are mainly expressed in the nervous system. Their fusions involve some 80 associated genes and they are known oncogenic drivers[35-38]. The incidence of *NTRK* fusions in NSCLC is estimated to be 0.1%-0.2%, affecting a population that is unselected in terms of sex, age, or smoking[37].

Currently, two first-generation TKIs targeting *NTRK* fusions have been approved by the FDA and the EMA: entrectinib (multikinase *ALK, ROS1,* and pan-*TRK* inhibitor) and larotrectinib (selective pan-*TRK* inhibitor). Both have demonstrated great efficacy (irrespective of histology or fusion gene) and intracranial activity, as well as good toxicity profiles[38-41].

Larotrectinib efficacy and safety in patients with solid tumours and *NTRK* fusions have been evaluated in two registrational phase I/II studies (NCT02122913 and NCT02576431). By July 2020, 20 patients with TRK fusion-positive lung cancer had been treated. Joint analysis of those studies, yielded an ORR of 73% and a CR rate of 7% for patients with lung cancer. The median PFS and OS in lung cancer patients was 35.4 and 40.7 mo. Among patients with baseline central nervous system metastases, the ORR was 63%. Reported adverse events were mostly grade 1-2[38].

Entrectinib was evaluated in the phase I ALKA-372-001 trial, phase I STARTRK-1 trial and phase II STARTRK-2 basket trial. For the 10 patients with NSCLC, the ORR was 70%, the CR rate was 10%, and PFS was 14.9 mo. Entrectinib showed a good toxicity profile; most adverse events were grade 1 or 2 and reversible, *e.g.*, dysgeusia, constipation, fatigue, diarrhoea, oedema, and dizziness[39].

Selitrectinib (LOXO 195), repotrectinib (TPX-0005), and taletrectinib (DS-6051b/AB-106) are second-generation drugs capable of inhibiting on-target resistance of *NTRK*[37,40]. They are currently being evaluated in phase I/II clinical trials in patients with *NTRK*-positive tumours who have progressed to first-generation inhibitors (NCT03215511, EudraCT 2017-004246-20, NCT04094610, TRIDENT-1: NCT03093116, NCT02279433).

HER2

HER2 is a cell growth promoting protein, a member of the *ERBB* family of tyrosine kinase receptors expressed on the surface of many types of tumours.

Overexpression, which occurs in 2%-20% of cases depending on the immunohistochemistry (IHC) level (IHC2+/3+), is associated with a poor prognosis. *HER2* amplification occurs, especially in adenocarcinomas, in around 3% of cases without prior treatment and in approximately 10% of cases of *EGFR* resistance to TKIs[42].

HER2 mutations *(HER2*m) – usually consisting of insertions in exon 20, especially in codon 776 – appear mainly in women, in adenocarcinoma cases, and in the Asian population, and never in smokers. The insertions cause constitutive activation of the receptor, making it sensitive to dual TKI action against *EGFR* and *HER2*, but not exclusively to *EGFR* inhibition[43].

The therapies commonly used to target *HER2* in breast cancer have not had the same results for NSCLC. The emergence of new TKIs and conjugated antibodies have given a new boost to therapies for this molecular alteration in NSCLC (Table 5). Reported for the largest retrospective EUHER2 study, which included patients with *HER2* exon 20 insertions, was an ORR of 7.4% for treatment with the TKIs afatinib, lapatinib, and neratinib; for the trastuzumab antibody and the trastuzumab emtansine (T-DM1) antibody-drug conjugate, the ORR was a more effective 50.9%, but that treatment was in most cases combined with chemotherapy[44,45].

Two phase II studies, of neratinib combined with trastuzumab in *HER2*m patients in first or successive therapy lines (NCT01953926) and of neratinib with temsirolimus (NCT01827267), have reported ORRs of 17% and 19%, respectively[46]. Zhou *et al*[47] explored the efficacy of pyrotinib in monotherapy, reporting an ORR of 30%, median PFS of 6.9 mo, and overall survival (OS) of 14.4 mo; the main toxicity, as with other *HER2*-targeting TKIs such as neratinib and lapatinib, was diarrhoea. In the phase II ZENITH20 trial of poziotinib, another pan-*HER* TKI, for the *HER2*m treatment the ORR was 28%, PFS was 5.5 mo, and the toxicity profile was similar to that for pyrotinib[48].

In addition to the *HER2* TKIs, also being evaluated in this setting are antibody-drug conjugates such as T-DM1 and trastuzumab deruxtecan (DS-8201, T-Dxd). Peters *et al*[49]. explored responses to TDM-1 in 49 patients with IHC2+/3+ overexpression, reporting no response for the IHC2+ cohort and 4 PRs for the IHC3+ cohort (20%). Better data is available for trastuzumab deruxtecan. For 42 patients with *HER2* m in the DESTINY-Lung01 cohort, the ORR was 62%, PFS was 14 mo; median OS was not achieved, while OS was 24.5% in the IHC2+/3+ overexpression cohorts[50].

To confirm the PFS benefit, a phase III trial of pyrotinib *vs* docetaxel called PYRAMID-1 (NCT04447118) is ongoing.

CONCLUSION

Compared to traditional chemotherapy, the improved TKI targeting of *EGFR* mutations and *ALK/ROS1* translocations has led to significant efficacy and quality of life improvements in the management of patients with NSCLC. While this subgroup of patients inevitably develops resistance to TKIs, this can be overcome by developing new next-generation TKIs or drugs aimed at overcoming resistance from the outset or from the time of discovery[51,52].

Table 5 Phase II trials with HER2 inhibitors

Drug	Molecular alteration	*n*	ORR%	PFS (mo)	OS (mo)
Dacomitinib[44]	HER2 mutant	26	12	NR	NR
	HER2-amplified	4	0	NR	NR
Neratinib + Trastuzumab[46]	HER2 mutant	52	17	4	10.2
Neratinib + Temsirolimus[46]	HER2 mutant	43	19	4	15.1
Pyrotinib[47]	HER2 mutant	60	30	6.9	14.4
Poziotinib[48]	HER2 mutant	90	28	5.5	NR
Trastuzumab emtansine[49]	IHC 2+	29	0	2.6	12.2
	IHC 3+	20	20	2.7	15.3
Trastuzumab deruxtecan[49]	HER-2 mutant	42	61.9	NR	NR
Trastuzumab deruxtecan[49]	IHC 2+	39	25.6	5.4	11.3
	IHC 3+	10	20		

ORR: Overall response rate; PFS: Progression free survival; OS: Overall survival; NR: Not reported.

These developments may also be transferable to the treatment of patients with other molecular alterations of *BRAF, KRAS, RET, MET, NTRK* and *HER2*. As can be seen above, a growing number of drugs and combinations are becoming available that target these alterations, often producing a significant improvement in response and survival rates.

Given the many common and rare molecular alterations in NSCLC, full-panel multigene NGS is recommended rather than gene-by-gene sequencing, as not only is it more cost-effective, it allows patients with a target to be easily identified and treated, whether with an approved drug or in a clinical trial of a promising drug[53-55].

FOOTNOTES

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